Comparative Effectiveness of Diuretic Regimens
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Acute decompensated heart failure is associated with substantial morbidity, mortality, and health care expenditures.¹ Most patients present with symptoms related to fluid overload, which may be complicated by concomitant renal dysfunction.² Treating the signs and symptoms of heart failure while preserving or improving renal function is a crucial therapeutic goal.

For more than five decades, the administration of intravenous loop diuretics has been the mainstay of therapy to reduce congestion, decrease ventricular filling pressures, and improve symptoms of heart failure, with such therapy becoming an empirically accepted standard of care for this condition.¹³⁴ However, there is little evidence from clinical trials to support this approach, and there are certain theoretical risks, including the risk of neurohormonal activation, systemic vasoconstriction, electrolyte disturbances, impairment of renal function, and perhaps, worse clinical outcomes.³⁵⁶ Establishing an evidence base that supports the appropriate use of intravenous loop diuretics and best balances safety and efficacy is warranted³; moreover, clinical-outcome trials to determine the effect of loop diuretics on mortality or the risk of rehospitalization are also necessary.

In this issue of the Journal, Felker and colleagues report the results of the Diuretic Optimization Strategies Evaluation trial (DOSE; ClinicalTrials.gov number, NCT00577135).⁷ This is the first trial to be reported by the National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network, which was created to conduct clinically useful, patient-centered investigations related to heart failure. The DOSE trial was a multicenter, randomized, controlled trial involving 308 patients who had been hospitalized for acute decompensated heart failure. The trial compared continuous intravenous infusion of the loop diuretic furosemide with administration of intravenous boluses every 12 hours and a low-dose strategy (in which a dose equal to the patient's previous oral dose was used) with a high-dose strategy (in which a dose 2.5 times the previous oral dose was used).⁷ The coprimary end points were patients' global assessment of symptoms and the change in the serum creatinine level from baseline to 72 hours. There was no significant difference in patients' global assessment of symptoms or in the mean change in serum creatinine level between the group receiving boluses and the group receiving continuous infusion. There was a numeric trend toward greater improvement in patients' global assessment of symptoms or in the mean change in serum creatinine level between the group receiving boluses and the group receiving continuous infusion. There was a numeric trend toward greater improvement in patients' global assessment of symptoms or in the mean change in serum creatinine level than in the low-dose group, but the difference did not reach significance. The patients in the high-dose group had greater relief of dyspnea and greater net fluid loss but were slightly more likely to have a transient worsening of renal function. The median length of stay in the hospital did not differ among the diuretic strategy groups.

What are the implications of this trial? The DOSE trial has importantly identified a lack of greater benefit with the diuretic regimen of continuous infusion — a regimen that is used frequently — than with a regimen of intermittent boluses. It also showed that, despite theoretical concerns and the findings of prior observational studies, a high dose of loop diuretics, as compared with a low dose, did not substantially worsen renal function. Both of these findings should change current practice. Since a high-dose regimen may relieve dyspnea more quickly with-
out adverse effects on renal function, that regimen is preferable to a low-dose regimen. Administration of boluses may be more convenient than continuous infusion and equally effective.

There are a number of other implications beyond those shown in the primary trial results. The DOSE trial raises the possibility that a global symptom assessment scale, which is a common research tool in this field, may be too insensitive to detect meaningful differences in symptoms. This trial also speaks to the potential of comparative-effectiveness research in a complex patient population receiving various background therapies. Nevertheless, since this trial was not powered to detect differences in the rates of death or rehospitalization, the effects of loop diuretics on clinical events in patients with heart failure remain unknown, despite the fact that these drugs have been in the treatment armamentarium for more than 50 years.

The DOSE trial also underscores the dismal prognosis for patients with acute decompensated heart failure. In this well-conducted study, performed at institutions that have highly regarded programs for patients with heart failure, there was an unacceptably high (43%) rate of death, rehospitalization, or emergency department visits within the first 60 days, irrespective of treatment assignment. Clearly, there is a crucial need to develop new agents and effective strategies for this patient population. Although a number of candidate agents (e.g., vasopressin antagonists, endothelin antagonists, adenosine antagonists, and nesiritide) have failed or have had equivocal results in recent trials, there remain promising treatment strategies and new agents that require critical testing in patients with acute decompensated heart failure. Should the primacy of loop diuretics be challenged by consideration of other means to relieve congestion? This too is being studied by the Heart Failure Clinical Research Network.

The study by Felker et al. of various dosing strategies for loop diuretics has not solved the problem of the poor prognosis for patients hospitalized with acute decompensated heart failure, nor has it modified the substantial expenditures for this disease. However, this study has introduced the new concept of comparative-effectiveness studies into the field of heart-failure research, high-lighting the importance of acquiring rigorous evidence, even for the most commonly applied interventions.

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